REMARKS

Claims 1-98 are currently pending. Claims 1-14 and 29-84 are withdrawn without prejudice or disclaimer. Claims 85-91 are canceled without prejudice or disclaimer. Applicants reserve their right to pursue the subject matter of any withdrawn and/or canceled claims in one or more continuing applications.

Claims 15-28 and 92-98 are currently presented for examination. Claims 15 is amended to remove the phrase "an effective amount of." Claims 15 and 23-28 are amended to remove the hyphen from the name "THAP-1." New claims 92-98 find support at page 59, line 31 to page 52, line 18 and elsewhere throughout the specification and claims as originally filed. Accordingly, no new matter has been added to the application.

After careful review of the instant Office Action, Applicants respectfully traverse the rejection of claims 15-28.

Rejection of claims 15-28 under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 15-28 under 35 U.S.C. § 112, second paragraph as allegedly "failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention" In particular, the Examiner asserts that the phrase "effective amount of agent comprising a polypeptide," as recited in claim 15, is unclear.

Applicants submit that the phrase "effective amount of agent comprising a polypeptide," as recited in claim 15, is clear to those of ordinary skill in the art. However, to expedite the allowance of claims 15-28, Applicants have deleted the phrase "an effective amount of" from claim 15.

In view of the foregoing amendment, the Examiner's rejection of claims 15-28 is moot. As such, Applicants respectfully request that the rejection of claims 15-28 under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejection of claims 15-28 under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejects claims 15-28 under 35 U.S.C. § 112, first paragraph as allegedly containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention." In particular, the Examiner asserts that the specification does not provide support for agents other than THAP1 or a chemokine-binding domain of THAP1 that inhibit the activity of a chemokine.

Applicants maintain that claims 15-28 are fully supported by the specification. Applicants would like to direct the Examiner's attention to Figure 8 of the specification. Figure 8 is a pictorial alignment of the domains of 12 human THAP-family polypeptides. The full-length sequence of each of these human THAP-family polypeptides is set forth in the sequence listing as SEQ ID NOs: 3-14. Additionally, the sequence listing describes the full-length sequences of at least 11 THAP-family polypeptides from organisms other than humans (SEQ ID NOs: 100-108, 110 and 113). A sequence alignment comparing each of these full-length polypeptides would show that these THAP-family proteins have from less than about 30% to greater than about 95% amino acid sequence identity to full-length THAP1 and include a sequence domain that has from less than about 30% to greater than about 95% amino acid sequence identity with the chemokine-binding domain of THAP1. Exemplary sequence alignments appear in Figures 1 and 10 of the instant application. Figure 1 provides an exemplary sequence alignment between SEQ ID NO: 3 (human THAP1) and SEQ ID NO: 99 (mouse THAP1). Over the full sequence length, the amino acid sequence identity between these two proteins is about 93%. When calculated for the chemokine-binding domain (corresponding to amino acids 143-213 of SEQ ID NO: 3), the amino acid sequence identity between these two sequences is between 95% and 96%. In Figure 10, the amino acid identity of human THAP1, THAP2 and THAP3 sequences is compared. Substantial amino acid identity (at least 30% amino acid identity) can be seen over the entire length of these proteins.

In addition to the foregoing examples, Applicants have described thousands of other sequences having at least 30% amino acid identity to THAP1 and having at least 30% amino acid identity to a chemokine-binding domain of THAP1. In particular, Applicants would like to draw the Examiner's attention to the text appearing at page 181, line 21 to page 182, line 18. This text is repeated below for the Examiner's convenience.

> By "chemokine-binding domain" or "portion that binds to a chemokine" is meant a fragment which comprises 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,

24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 160, 170, 180, 190, 200, 210 or greater than 210 consecutive amino acids of a THAP-family polypeptide but less than the total number of amino acids present in the THAP-family polypeptide. In some embodiments, the THAP-family polypeptide is THAP-1 (SEQ ID NO: 3).

The complete amino acid sequence of each human THAP-family polypeptide is described in the Sequence Listing. In particular, THAP-1 is (SEQ ID NO: 3), THAP-2 is (SEQ ID NO: 4), THAP-3 is (SEQ ID NO: 5), THAP-4 is (SEQ ID NO: 6), THAP-5 is (SEQ ID NO: 7), THAP-6 is (SEQ ID NO: 8), THAP-7 is (SEQ ID NO: 9), THAP-8 is (SEQ ID NO: 10), THAP-9 is (SEQ ID NO:11), THAP-10 is (SEQ ID NO: 12), THAP-11 is (SEQ ID NO: 13), THAP-0 is (SEQ ID NO: 14). The complete amino acid sequence of additional THAP-family polypeptides from other species are also listed in the Sequence Listing as SEQ ID NOs: 16-98. As such, the chemokine-binding portion of any of these THAP-family polypeptide sequences that are listed in the Sequence Listing is explicitly described. In particular, in some embodiments, the chemokine-binding domain is a fragment of a THAP-family chemokine-binding agent described by the formula:

> for each THAP-family polypeptide, N = the number of amino acids in the full-length polypeptide; B = a number between 1 and N – 1; and E = a number between 1 and N.

For any THAP-family polypeptide, a chemokine-binding domain is specified by any consecutive sequence of amino acids beginning at an amino acid position B and ending at amino acid position E, wherein E > B.

As such, the instant specification describes all possible portions or fragments of any of the THAP-family polypeptides described therein. To put this into perspective, consider the full-length, human THAP1 polypeptide of SEQ ID NO: 3. This polypeptide has 213 amino acids. Applying the formula above, the specification also describes related polypeptides having amino acids 1-212 of SEQ ID NO: 3, amino acids 1-211 of SEQ ID NO: 3, amino acids 1-210 of SEQ ID NO: 3, amino acids 2-213 of SEQ ID NO: 3, amino acids 3-213 of SEQ ID NO: 3, amino acids 2-212 of SEQ ID NO: 3, amino acids 3-212 of SEQ ID NO: 3, amino acids 3-211 of SEQ ID NO: 3, and so on. Sequence fragments having greater than 63 amino acid residues will have at least 30% amino acid identity to the full-length, human THAP1 polypeptide. Furthermore, the formula can also be applied to any THAP-family polypeptide described in the specification so as to generate a thousands of polypeptides having at least 30% amino acid identity to THAP1 or having at least 30% amino acid identity to a chemokine-binding domain of THAP1.

In addition to the thousands of polypeptides having at least 30% amino acid identity to THAP1 or having at least 30% amino acid identity to a chemokine-binding domain of THAP1 discussed above, Applicants have also described inhibiting the activity of numerous chemokines using THAP1, polypeptides having at least 30% amino acid identity to THAP1, a chemokine-binding domain of THAP1 and polypeptides having at least 30% amino acid identity to a chemokine-binding domain of THAP1. In particular, the specification, at page 115, lines 10-26, states the following:

> It will be appreciated that THAP-type chemokine-binding agents will be used for applications which include, but are not limited to, chemokine binding, inhibiting or enhancing chemokine activity, chemokine detection, reducing the symptoms associated with a chemokine influenced or mediated condition, and reducing or preventing inflammation or other chemokine mediated conditions. THAP-type chemokine-binding agents can also be used in the kits, devices, compositions, and procedures described elsewhere herein.
>
> In some embodiments of the present invention, THAP-type chemokine-binding agents bind to or otherwise modulate the activity of one or more chemokines

selected from the group consisting of XCL1, XCL2, CCL1, CCL2, CCL3, CCL3L1, SCYA3L2, CCL4, CCL4L, CCL5, CCL6, CCL7, CCL8, SCYA9, SCYA10, CCL11, SCYA12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27, CCL28, clone 391, CARP CC-1, CCL1, CK-1, regakine-1, K203, CXCL1, CXCL1P, CXCL2, CXCL3, PF4, PF4V1, CXCL5, CXCL6, PPBP, SPBPBP, IL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL14, CXCL15, CXCL16, NAP-4, LFCA-1, Scyba, JSC, VHSV-induced protein, CX3CL1, and fCL1.

THAP-type chemokine-binding agents are defined at page 192, lines 8-15 to include, among other things, THAP1, polypeptides having at least 30% amino acid identity to THAP1, a chemokine-binding domain of THAP1 and polypeptides having at least 30% amino acid identity to a chemokine-binding domain of THAP1.

In addition to the foregoing description, specific examples of chemokine-binding by THAP1, polypeptides having at least 30% amino acid identity to THAP1, a chemokine-binding domain of THAP1 and polypeptides having at least 30% amino acid identity to a chemokine-binding domain of THAP1 are also described in the specification. For example, chemokine binding to specific deletion fragments of human THAP1 (amino acids 1-213 of SEQ ID NO: 3) is shown in Figure 12. In particular, Figure 12 shows that full-length THAP1, sequence fragments comprising the THAP1 chemokine-binding domain (e.g., amino acids 90-213, amino acids 120-213 and amino acids 143-213) and certain THAP1 variants (e.g., full-length THAP1 having the double mutation R171A and R172A) have the ability to bind SLC/CCL21. Another example of chemokine binding is shown in Figure 19, which displays the results of the experiments described in Examples 32 and 33 . Specifically, Figure 19 shows that THAP1 interacts with both CC-family chemokines (CCL21, CCL19, CCL5) and CXC-family chemokines (CXCL9 and CXCL10) both *in vivo* in a yeast two-hybrid system with THAP1 prey and *in vitro* using GST-pull down assays with immobilized GST-THAP1.

In view of the foregoing discussion, it is clear that the specification provides sufficient disclosure to support the full scope of claims 15-28. Applicants would like to remind the Examiner that written description jurisprudence does not require that an applicant supply

experimental evidence in order to support a claim. While it is true that an applicant can utilize experimental evidence, such as working examples, to provide written description to support claims, neither the statute nor the case law requires this. To put it another way, in the analysis of whether an applicant has met the written description requirement, the question of whether working examples are provided is irrelevant. Rather, Applicants must describe a representative number of species to support the claimed genus. Here, Applicants have described thousands of species of polypeptides having at least 30% amino acid identity to THAP1, and thousands of species of polypeptides having at least 30% amino acid identity to a chemokine-binding domain of THAP1. Furthermore, Applicants have described inhibiting the activity of chemokines using these thousands of species of polypeptides having at least 30% amino acid identity to THAP1 and thousands of species of polypeptides having at least 30% amino acid identity to a chemokine-binding domain of THAP1. As such, Applicants have provided a representative number of species to support the claimed genera.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of claims 15-28 under the written description requirement of 35 U.S.C. § 112, first paragraph.

Rejection of claims 15-28 under U.S.C. § 112, first paragraph (enablement)

The Examiner rejects claims 15-28 under 35 U.S.C. § 112, first paragraph as allegedly encompassing subject matter that is not enabled by the specification. The Examiner does acknowledge that the specification enables "a method of inhibiting SLC/CCL21 activity using the THAP1 chemokine-binding domain and inhibiting CCL5 and SLC/CCL21 activity using the THAP1 protein (SEQ ID NO: 3), however, the Examiner asserts that the specification does not provide enablement for (a) using polypeptide variants of THAP1 having 30% amino acid identity to inhibit the activity of chemokine CCL5 and SLC/CCL21, and (b) using a chemokine-binding domain of THAP1 to inhibit the activity of any chemokine other than CCL5 or SLC/CCL21.

Applicants maintain that claims 15-28 are fully enabled by the specification. As discussed above, the specification describes THAP1 polypeptides and THAP1 chemokine-binding domains from numerous organisms as well as thousands of species of polypeptides having at least 30% amino acid identity to THAP1 and thousands of species of polypeptides

having at least 30% amino acid identity to a chemokine-binding domain of THAP1. For non-naturally occurring THAP1 and THAP1 chemokine-binding domain homologs, the specification describes routine preparation methods using well known deletion and mutagenesis methods (see page 99, line 23 to page 107, line 32).

In addition to the foregoing teachings, the specification provides working examples (Examples 15-17, 32 and 33), that demonstrate how to test the binding of chemokines to full-length THAP1, chemokine-binding domains of THAP1, polypeptides having at least 30% amino acid identity to THAP1 and polypeptides having at least 30% amino acid identity to a chemokine-binding domain of THAP1. Specifically, these working examples show that THAP1 and homologs thereof as well as the chemokine-binding domain of THAP1 and homologs thereof bind to various chemokines, including CCL21, CCL19, CCL5, CXCL9 and CXCL10 (see Figures 12 and 19). Generally, these examples describe routine procedures that one of ordinary skill in the art can use to determine whether any THAP1 polypeptide, polypeptide having at least 30% amino acid identity to THAP1, chemokine-binding domain of THAP1 and/or polypeptide having at least 30% amino acid identity to a chemokine-binding domain of THAP1, including the thousands of polypeptides described in the specification, binds to one or more chemokines. Indeed, Applicants have used these very methods to determine the specificity of chemokine binding to the chemokine-binding domains of human THAP2 and human THAP3 (see Example 38 and Figures 21A-E and 22A-C of copending U.S. Patent Application No. 11/360,450, which claims priority to the instant application).

Assays for determining the effect of THAP1, chemokine-binding domains of THAP1, polypeptides having at least 30% amino acid identity to THAP1 and polypeptides having at least 30% amino acid identity to a chemokine-binding domain of THAP1 on chemokine activity are described in Examples 34-37. Again, Applicants have used these routine methods to demonstrate that that such polypeptides inhibit the chemokine activity in both *in vitro* and *in vivo* assays (see Examples 41-43 of copending U.S. Patent Application No. 11/360,450, which claims priority to the instant application).

Applicants would like to remind the Examiner that undue experimentation is not measured by the amount of time, expense or quantity of routine experimentation that is involved in implementing the disclosed methods. (see *In re Wands* 858 F.2d 731 (Fed. Cir. 1988); *United*

States v. Telectronics Inc., 857 F.2d 778 (Fed. Cir. 1998); and M.P.E.P. § 2164.06). Provided that the procedure used to implement the claimed invention routine, it is of little consequence to enablement the number of iterations or the length of the procedure that is required before the end is achieved. As described above, Applicants have provided detailed guidance describing how to obtain THAP1 polypeptides, polypeptides having at least 30% amino acid identity to THAP1, chemokine-binding domains of THAP1 and polypeptides having at least 30% amino acid identity to a chemokine-binding domain of THAP1, and further how to test these polypeptides to determine their ability bind chemokines and inhibit chemokine activity. All of the methods used to obtain and test these polypeptides are known in the art and fully described in the specification. As such, only routine experimentation is required to determine which additional THAP1 polypeptides, polypeptides having at least 30% amino acid identity to THAP1, chemokine-binding domains of THAP1 and polypeptides having at least 30% amino acid identity to a chemokine-binding domain of THAP1 inhibit the activity of one or more chemokines.

In view of the above remarks, Applicants respectfully request that the Examiner withdraw the rejection of claims 15-28 as lacking enablement under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants believe that all outstanding issues in this case have been resolved and that the present claims are in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact the undersigned at the telephone number provided below in order to expedite the resolution of such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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